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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/238,741 | 01/28/1999 | GARY R. BRASLAWSKY | 012712-584 | 5956 |

909 7590 12/22/2003
PILLSBURY WINTHROP, LLP
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MCLEAN, VA 22102

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| EXAMINER |
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HELMS, LARRY RONALD

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| ART UNIT | PAPER NUMBER |
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1642

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

| | | |
|-----------------|-------------------|--|
| Application No. | Applicant(s) | |
| 09/238,741 | BRASLAWSKY ET AL. | |
| Examiner | Art Unit | |
| Larry R. Helms | 1642 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-9,14,24-29,34-36,41,45-48 and 50-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-9,14,24-29,34-36,41,45-48 and 50-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Claims 1-2, 4-9, 14, 24-29, 34-36, 41, 45-48, 50-60 are pending and under examination. The amendment filed 10/3/03 added claims 50-61, however, the claims did not include a claim 59 and as such claims 60-61 have been renumbered under Rule 1.126 as 59-60, respectively.

Claims 14, 35 have been amended.

2. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.
3. The following Office Action contains NEW GROUNDS of rejections.

Rejections Withdrawn

4. The rejection of claim 14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claim.

Response to Arguments

5. The rejection of claim 36 (previously as claim 35 in this rejection by mistake) under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained.

The response filed 10/3/03 has been carefully considered but is deemed not to be persuasive. The response states that the amino acid of the light and heavy chains of the C2B8 including the human kappa and gamma constant regions are disclosed in Figures 1A and 2A and complete DNA sequences are in US Patent 5,736,137 and the heavy and light chains of p5E8 are in US Patent 6,011,138. In response to this argument, while the heavy and light chains are disclosed in the patents the entire amino acid sequence such as the hinge, CH2, CH3, sequences are not and therefore the entire sequence is not disclosed. As such the deposit is still required because it is still not clear if the hybridomas that produce the antibodies are commercially available. The claims require the entire antibodies and the specification teaches combining the molecules but the molecules themselves are required for the practice of the invention.

Response to Arguments/NEW GROUNDS of rejection

6. The rejection of claims 1-2, 4-9, 14, 24-29, 34-36, 41, 45-48, 50-60 under 35 U.S.C. 103(a) as being unpatentable over Caron et al (J. Exp. Med. 176:1191-1195, 1992, PTO-892) and further in view of Fanger et al (Critical Reviews in Immunology 12:101-124, 1992, PTO-892) and Cumber et al (J. Of Immunol. 149:120-126, 1992, PTO-892) and Reff et al [a] (U.S. Patent 6,011,138, filed 2/20/97, PTO-892) and Reff et al [b] (Blood 83:435-445, 1994, PTO-892) and The Pierce Catalog (pages T-157, T-163-169, 1994-95) is maintained.

The response filed 10/30/03 has been carefully considered but is deemed not to be persuasive. The response states that the specification describes the method of providing a 100% increase in yield over such a method described in Caron et al which

does not include the step of contacting the antibody with a reducing agent to partially reduce the disulfide bonds and at the time of the invention it was known that reducing agents reduce and cleave intra and interchain disulfide bonds and persons skilled in the art would reasonably have avoided contacting antibodies with reducing agents prior to dimerization in order to prevent the disassembly of the antibodies into their component peptides. In response to these arguments, Cumber clearly teaches reducing the disulfide linked dimers to monomers prior to producing a bispecific antibody molecule (see page 121, right column). The FV molecule of Cumber has disulfide bonds in the variable and constant region and Cumber reduces the molecule prior to formation of the bispecific molecule to prevent dimer formation between the molecules with the same specificity. Reduction does not alter the structure of the molecules and as such one would conclude that one could reduce the molecule of Caron. Therefore, it would have been obvious to reduce the molecule of Caron by the method of Cumber to result in only bispecific molecules and reduce the bifunctional molecules that are monospecific. In addition, the Pierce Catalog teaches heterobifunctional crosslinkers for conjugation of proteins and the heterobifunctional crosslinkers have the advantage of minimizing undesirable polymerization or self-conjugation which would result in a higher purity of the heterodimeric product and not the undesirable product of a homodimer as is needed in the claims.

In addition claims 45-46 and newly submitted claims 50-60 do not require reduction of any antibody and therefore, arguments directed to such is not persuasive.


Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references. \

Conclusions

7. No Claims are allowed.
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.
9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.



LARRY R. HELMS, PH.D.
PRIMARY EXAMINER

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703-306-5879